



COMBINATION PRODUCT COALITION

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

**RE: Comments on Draft Guidance for Industry and FDA: Current
Good Manufacturing Practice for Combination Products, Food
and Drug Administration Docket No. 2004D-0431**

Dear Sir or Madam:

The Combination Products Coalition ("CPC") respectfully submits for consideration these comments on the Food and Drug Administration's ("FDA") Draft Guidance on Current Good Manufacturing Practice for Combination Products (the "Draft Guidance"). The CPC is a group of leading pharmaceutical, biologics, and medical device manufacturers with substantial experience in the combination products arena, as well as in each of the constituent technologies. Because of its diverse membership, the CPC brings a uniquely broad and experienced perspective to the problems of regulating combination products. With that background in mind, we offer the following comments.

I. General Comments

The CPC applauds the FDA's effort in crafting this Draft Guidance, which provides a good start to tackling the difficult problems that arise with application of Current Good Manufacturing Practices ("CGMP") and Quality System ("QS") regulations to combination products. We believe the Draft Guidance, which approaches the issues from the

"hundred-thousand foot" level, is the right place to begin the complex task of working through the plethora of issues raised by applying two or more distinct sets of regulations to one product. It is the beginning, however, not the end. With the diverse array of combination products that fall within the agency's scope, the only way for FDA to achieve consistency in application of CGMP and QS regulations is to develop a number of specific guidances to address the variety of issues raised. With that in mind, we urge FDA to continue its efforts, and to develop more specific guidance on application of CGMP and QS regulations to combination products.

That said, the purpose of these comments is to identify specific areas in which FDA's approach needs further clarification or revision. Our goal is to ensure predictable, transparent, and consistent application of the guidances that ultimately apply to the manufacturing of combination products. To that end, we offer the following specific comments.

II. Specific Comments

A. FDA needs to clarify impact of assignment on application of CGMP and QS regulations

One of the most critical issues impacting application of CGMPs and QS regulations to combination products is whether, and to what extent, FDA will allow assignment of a lead center to drive the determination of what CGMPs and QS regulations should apply to a particular combination product. As discussed in the CPC's *Response to Request for Comment on Primary Mode of Action* filed with the FDA on August 18, 2004,¹ and raised again in the CPC's comments on the *Draft Guidance for Industry and FDA Staff: Application User Fees for Combination Products*, filed with the agency on November 24, 2004, we believe that FDA needs to clarify its view of what assignment to a particular agency component means before FDA proceeds with issuing further regulations or guidance. If FDA adopts the view that assignment determines not only who will take the lead, but also which authorities and obligations will apply, that has tremendous implications on downstream regulation. The application of good manufacturing and quality systems regulations are just the start – albeit an important one.

The Draft Guidance provides a good example of the impact that the assignment issue can have in practice. Although it is not clear from the Draft Guidance what role the FDA intends the lead center to play in determining which regulations will apply to a given combination product, the Draft Guidance seems to suggest that FDA intends for the lead center to oversee regulation of a combination product. Presumably, that could include determination of which manufacturing and quality system regulations apply. However, the Draft Guidance also allows that compliance with CGMPs and QS regulations can generally be achieved "by using the current good manufacturing practice system already operating at a manufacturing facility."² Indeed, under the Draft Guidance, the manufacturer's pre-existing current good manufacturing practice system (referred to in the Draft Guidance as the "Operating Manufacturing Control System") would be a major factor in deciding which regulation sets the overall, general quality system for a particular

combination product. The other regulations would be incorporated in a subordinate capacity to address specific issues that may be pertinent to one of the product's components.³ Giving the lead center ultimate authority over regulations applicable to the manufacturing of a combination product very well could negate this provision – which is the foundation of the guidance's approach. Instead, the lead center for each combination product would control. Consider the potential inconsistencies:

- For a device manufacturer that manufactures a drug/device combination product, the Operating Manufacturing Control System in place likely would be based on QS regulations applicable to medical devices. Scale up of those manufacturing facilities, therefore, would likely be handled under the device regulations, and no filing may be required.
- If however, CDER is assigned as lead center for the drug/device combination and given ultimate control over regulation, CDER might require that scale-up of the manufacturing facilities be handled under the drug authorities. If so, CDER could require the manufacturer to file a supplemental NDA to accommodate the change.

This need not be the case, though. FDA has made very clear that, although the statute provides a mechanism for determining which agency component will take the lead on review of a particular combination product, it did not provide a similar mechanism for determining which regulatory authorities will apply. Instead, Congress chose to rely on FDA's expertise to determine which regulatory authorities should apply to a given combination product.⁴ We urge FDA not to take that responsibility lightly.

With that in mind, the CPC disagrees strongly with allowing assignment to a lead center to control the complex question of which regulations apply downstream, and believes that such a determination would lead to inconsistent and unintended outcomes. For this reason, we exhort FDA to make a clear and unambiguous statement of its intent.

B. FDA should reconsider its case-by-case approach to regulation of specific combination products

Generally, we believe that FDA's case-by-case approach to regulation of specific combination products outlined in the Draft Guidance misses the mark. FDA has stated time and again that it intends to develop regulations and guidance that ensure consistency, predictability and transparency of combination product regulation. The outlined approach cannot achieve that goal. With the wide variety of combination products to be covered by the Draft Guidance, and thousands of custom-tailored systems likely to result, there is an incredible potential for disparity in regulatory treatment among similar combination products. In addition, without more direct and specific guidance, word of mouth among reviewers and investigators may lead to misapplication of similar, generalized principles to very different combination products.

We understand and appreciate that, in the world of combination products, one size does not fit all. In fact, in our white paper submitted to FDA in April 2004,⁵ the CPC commented on the need for flexibility in defining quality systems and good manufacturing practice requirements for various types of combination products, since each combination is different and may involve widely different development and production processes. However, the current approach goes too far, exchanging flexibility for customization. Instead, we recommend that FDA develop specific guidance to address the particular manufacturing and quality systems issues that arise with different types of combination products. The only way to ensure consistency, predictability and transparency is to specify the rules. Only then can manufacturers be assured that: (1) They know and are complying with the rules; and (2) they are complying with the same rules as their competitors.

1. At the very least, FDA should consider putting procedural safeguards in place

Although we strongly believe that FDA's current approach fails to meet FDA's goals, we understand that FDA may disagree with our assessment. For that reason, should FDA continue down the path described in the Draft Guidance, we offer the following suggestions.

If FDA follows the case-by-case approach enumerated in the Draft Guidance, the agency needs to elaborate a set of basic procedural norms that will be followed in all such discussions. This will provide at least some level of assurance to manufacturers that they are on a level playing field and promote public confidence in the integrity of combination-products regulation.

To that end, we believe that, at a bare minimum, the Draft Guidance needs to provide additional procedural detail to clarify how this process might work for various types of combination products. For instance: What are the specific pathways for initiating and conducting these discussions? How can sponsors ensure they are involved in all relevant discussions with FDA staff? What data and submissions may be required for different products that involve different combinations of the regulations? What information will FDA require a manufacturer to submit in support of its proposed CGMP/QS plan? What are the standards for determining the adequacy of manufacturers' proposals? Are there indicative time lines for processing manufacturers' requests? What are the end-points of these discussions, e.g., will the results of these discussions be memorialized in a letter of agreement or other record on which manufacturers can rely in planning their ongoing operations? FDA should include guidance to address all of these questions.

We recognize that the diversity of combination products makes it very hard to outline a single procedural pathway that will be appropriate in every instance. With that in mind, to clarify the appropriate procedures for conducting discussions between FDA and

manufacturers, it may be necessary for the Draft Guidance to elaborate multiple pathways and criteria for determining which combination products appropriately belong on which procedural pathway. The Draft Guidance should consider a number of indicative example products, clarify how these procedures might actually work for each of them, and enunciate the key factors FDA will consider in determining what process is appropriate for a given combination product.

In addition, to ensure at least some level of transparency in the process, we encourage FDA to publish its CGMP/QS decisions, with as much supporting documentation as possible. While we understand that confidentiality concerns may prevent sharing of all of the information exchanged between manufacturers and FDA, it is critical that FDA provide easy access to at least basic information to give the industry a sense of how FDA might apply the rules in a given circumstance. Along these same lines, we suggest that FDA provide an interactive webpage for manufacturers, with a feature that enables manufacturers to ask FDA questions, and receive answers. Posting of questions and answers on the webpage would provide an additional opportunity for bringing transparency to the process.

C. FDA should specify which regulations will apply to different types of combination products

We believe that FDA's simultaneous application of CGMPs and QS regulations to combination products is unnecessary and impractical to achieve. Instead, we believe that FDA should: (1) Apply appropriate regulations to *each constituent component* of the combination product as long as the manufacturer can distinguish between the components of the product; and (2) if constituent components become indistinguishable (which may happen with respect to some integral combination products that are formed into a unit), specify which of the CGMP regulations and which of the QS regulations will apply to that type of combination product. We discuss this approach in greater detail below.

1. FDA should apply the appropriate regulations to each constituent component as long as they are distinguishable

We believe that FDA should apply the appropriate regulations to each constituent component of a combination product – even if the products are joined together – as long as the constituent components remain distinguishable. As currently written, the Draft Guidance applies device QS regulations to device components and drug CGMPs to drug components, until the components become one. The Draft Guidance provides that, for integral and kit combination products, “both sets of current good manufacturing practice regulations are applicable during and after joining the constituent parts together.”⁶

The concept of “during and after joining,” while simple on its face, assumes too much. It assumes that there is some clear point at which the constituents of a combination product merge, and that only at that point do both

regulatory schemes become relevant. In practice, however, there may not be a finite point in time at which the constituents join as a product. Instead, they may retain their individual constituent character throughout the manufacturing process (as in the case of virtual combination products and some kits).

- For example, the constituent components of a drug and delivery system – such as an IV pump -- can maintain their individual constituent character, even after being combined.

Conversely, the nature of the constituent parts may trigger consideration of *both* regulatory schemes even *prior to joinder*. Consider how this example from FDA's archives might be handled:

- FDA determined that, although a catheter flush solution containing a blood-thinning drug and an antibiotic combined with a catheter had a primary mode of action that was "physical in nature," and typically would be subject to review by CDRH, the innovative aspects of the solutions raised important scientific and regulatory questions that were more appropriately reviewed by CDER.⁷ FDA had clinical investigations of the product proceed under the investigational drug provisions of the statute. Since the combination product was being treated as a drug – would drug CGMPs control, or would QS regulations (including design controls) apply to the catheter component?

As this example illustrates, if it is known that a given constituent is destined to be "joined" into a particular combination product, it may be necessary to take certain steps even before any such joinder, to lay the groundwork for compliance with regulatory requirements that will later come into force. Given these practicalities, the concept of "during and after joinder" may be too simple to work in practice.

As an alternative, we believe that FDA should provide for appropriate regulation of each of the constituent components, as long as they are distinguishable. What is *appropriate*, however, should depend on the type of combination product involved. In many (likely most) cases, a device component should be subject only to device QS regulation until such time as the device is no longer distinguishable from the other constituent components of a combination product. Depending on the nature of the combination product, *appropriate* regulation may require the incorporation of certain regulations from the drug CGMP scheme to ensure patient safety of the ultimate combination product. We do not advocate duplicative or parallel regulation; rather, we encourage FDA to choose appropriate regulations depending on the type of combination product involved.

As discussed in our April 2004 White Paper, a case-study approach may be the best way to identify and address these subtleties. This would involve looking at development and production processes for various example products,

considering the CGMP/QS issues that may arise at various points in these processes, and specifying the appropriate combination of regulations that apply at various stages. Again, this requires much more specific guidance than FDA has provided in the DRAFT Guidance

2. If constituent components become indistinguishable, specify which of the CGMP regulations and which of the QS regulations will apply

Even when there may be a temptation to apply dual CGMP and QS requirements to a particular combination product – as when the components become indistinguishable -- we believe FDA must make choices among which regulations should apply. Attempting to mesh the CGMP regulations and QSR requirements into one common regulatory scheme is tantamount to fitting a square peg into a round hole. It ignores the purpose and shape of the underlying regulations. For instance, the device QS regulations reach farther “upstream” into the design process than the drug CGMP regulations reach. As a result, manufacturers otherwise subject to CGMP regulation may find that their existing Operating Manufacturing Control Systems do not have appropriate upstream “slots” into which the device requirements can be fit. Blanket application of both sets of regulations may provide a simple answer, but it falls short in implementation. FDA needs to choose which regulations will apply, under what circumstances.

Once again, we believe that the answer is to provide specific guidance on which QS and which CGMP regulations apply to particular types of combination products. Using case studies and examples, FDA could go a long way toward simplifying the process for the agency and industry alike.

D. Training and Personnel Development

As discussed in our April 2004 White Paper, because of the complexity of the different CGMP and QSR systems for biologics, drugs and devices, appropriate regulation and enforcement of combination products will require cross-training of inspectors, or in some instances, inspection by a team of two or more inspectors with complementary skills and experience. The Draft Guidance does not yet address the important question of how compliance inspections may differ for different types of combination products: *e.g.*, What are likely to be the criteria for determining whether a given CGMP/QSR system can be adequately inspected by a single inspector with cross-training, as opposed to needing separate inspections of its CGMP and QSR components? Will the “lead” inspection personnel vary, depending on the assignment of the lead center for regulating a particular combination product? How will the FDA ensure consistent treatment of similar products? What role can manufacturers usefully play in developing appropriate solutions and in exchanging ideas related to training and development of personnel? These questions should be addressed in, or in parallel with, the Draft Guidance.

III. Conclusion

We appreciate FDA's efforts in preparing this Draft Guidance, and believe it is the right place to start. The next step, however, is critical. We firmly feel that FDA needs to provide more specific guidance on how CGMP and QS regulations will be applied to particular types of combination products, using case studies and examples to illustrate the agency's thinking. FDA has a tremendous opportunity to use its scientific expertise and experience to craft thoughtful and practical guidelines that will ensure consistent and predictable application of the regulations. This should be familiar ground for FDA, and we urge the agency to take this step. We stand ready to assist in any way we can.

We appreciate this opportunity to present our comments on the Draft Guidance, and look forward to working with FDA as the agency moves forward.

Respectfully Submitted,



Bradley Merrill Thompson
For the Combination Products Coalition

¹ (Letter from Bradley Merrill Thompson, Combination Products Coalition, to FDA of August 18, 2004, regarding Response to Request for Comment on Primary Mode of Action, Food and Drug Administration Docket Number 2004N-0194).

² FDA, *Guidance for Industry and FDA, Current Good Manufacturing Practice for Combination Products*, at 5 (September 2004).

³ See Draft Guidance at 6, Table 1.

⁴ See *Final Rule, Regulations Restricting the Sale and Distribution of Cigarettes and Smokeless Tobacco to Protect Children and Adolescents*, 61 Fed. Reg. 44396, 44400 (August 28, 1996) (Discussing in general FDA's discretion to determine which regulatory authorities apply to combination products).

⁵ Combination Products Coalition, *Combination Products: Proposed Policies to Enhance the FDA Regulatory Process* (Submitted to the FDA in April, 2004).

⁶ Draft Guidance at 5.

⁷ Final Tobacco Rule, 61 Fed. Reg. at 44403.